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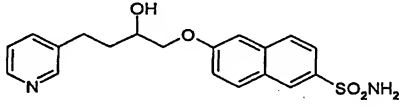
(54) Title: NOVEL COMPOUNDS

(57) Abstract

The invention relates to novel pyridyl derivatives (I), their use as medicaments, pharmaceutical formulations including them and methods for their preparation.



(I)

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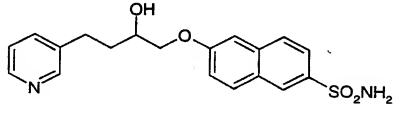
NOVEL COMPOUNDS

This invention relates to novel pyridyl derivatives, their use as medicaments, pharmaceutical formulations including them and methods for their preparation.

PCT Patent Application PCT/SE98/00423 discloses certain pyridine alkanol derivatives having activity as mast cell antagonists.

It has now surprisingly been found that a compound within the scope of PCT/SE98/00423 but not specifically disclosed therein exhibits advantageous pharmacokinetics and physical properties. For example, the compound had improved physical properties which led to a reduced plasma binding in blood and increased systemic exposure.

In a first aspect the present invention therefore provides a compound of formula (I) or a salt thereof:



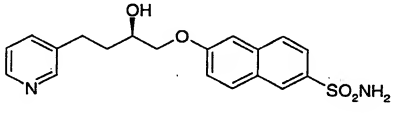
(I)

The compound of the invention can form pharmaceutically acceptable solvates and salts. The compounds of the formula (I) can form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric and methanesulphonic acids. Compounds of the invention may also form alkali metal salts such as magnesium, sodium, potassium and calcium salts.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms including enantiomers and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by

stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

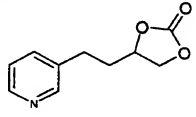
Preferably the compound of formula (I) has the stereochemistry shown below:



(I)

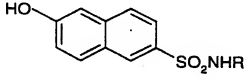
The compound of formula (I) can be prepared using the methods described in PCT/SE98/00423.

Therefore the invention also provides a process for the preparation of compounds of formula (I) as hereinbefore defined which comprises:
(a) reaction of a compound of formula (II):



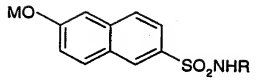
(II)

with a compound of formula (III):



(III)

where R is a suitable protecting group such as tertiary butyl
(b) reaction of (±)-3-(2-oxiranylethyl)pyridine or α-(chloromethyl)-3-pyridinepropanol either with a compound of formula (IV):



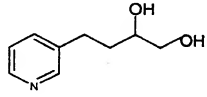
(IV)

where R is as defined above and M is Li, Na, K or MgHal where Hal is halogen, for example at ambient or elevated temperature in a suitable solvent such as dimethylformamide or tetrahydrofuran;
or with a compound of formula (II) as defined above in the presence of a base such as sodium hydroxide in a suitable solvent such as aqueous ethanol, or
and optionally thereafter (a) or (b):

- removing any protecting groups, and/or
- forming a pharmaceutically acceptable salt.

Reaction of compounds of formulae (II) and (III) can be carried out the presence of a suitable base in an inert solvent at elevated temperature, for example using cesium carbonate in dimethylformamide at about 100°C.

Compounds of formula (II) can be prepared by treating compounds of formula (V):



(V)

with 1,1'-carbonyldiimidazole. The reaction can be carried out in a solvent such as chloroform at elevated temperature, preferably at reflux temperature.

Compounds of formula (IV) and (V) are commercially available or can be prepared using known techniques. It will be appreciated by those skilled in the art that in the process described above the functional groups of intermediate compounds may need to be protected by protecting groups.

Functional groups which it is desirable to protect include hydroxy and sulfonamide. Suitable protecting groups for hydroxy include organosilyl groups (e.g.

tert-butyldimethylsilyl, *tert*-butyldiphenylsilyl or trimethylsilyl), benzyl and tetrahydropyranyl. Suitable protecting groups for sulfonamide include alkyl groups, in particular tertiary butyl.

The protection and deprotection of functional groups may take place before or after a reaction step.

The use of protecting groups is fully described in 'Protective Groups in Organic Chemistry', edited by J. W. F. McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 2nd edition, T. W. Greene & P. G. M. Wutz, Wiley–Interscience (1991).

Novel intermediates form a further aspect of the invention. In particular the compound 6-(2-hydroxy-4-pyridin-3-yl-butoxy)-naphthylene-2-sulfonyl *tert*-butylamide forms an aspect of the invention.

Diastereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The various optical isomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. fractional crystallisation or HPLC, techniques.

The compounds of the invention are useful because they possess pharmacological activity and more particularly activity in the modulation of inflammatory and allergic conditions, for example as shown in the test described below. The compounds of the invention inhibit the activation of a range of cell types from haematopoetic lineage, including mast cells, neutrophils and eosinophils. In a further aspect the invention therefore provides a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use in therapy.

The compounds of the invention are indicated for use in the treatment or prevention of allergic, inflammatory, auto-immune, proliferative and hyper-proliferative diseases.

The compounds of the invention are also indicated in the treatment and prevention of allergic, inflammatory or auto-immune conditions of the lung, including reversible obstructive airways diseases which includes asthma (e.g. bronchial, allergic, intrinsic asthma, extrinsic and chronic asthma), and associated manifestations of the disease (late responses, hyper-responsiveness), also farmer's lung and related diseases, fibrosis,

ideopathic interstitial pneumonia, chronic obstructive airways disease (COPD), bronchiectasis, cystic fibrosis, eosinophilic pneumonias, adult respiratory distress syndrome (ARDS), emphysema and alveolitis, for example cryptogenic fibrosing alveolitis.

Further, the compounds of the invention are indicated in the treatment or prevention of allergic, inflammatory or auto-immune conditions in the nose including all conditions characterised by inflammation of the nasal mucous membrane such as acute rhinitis, allergic rhinitis, atrophic rhinitis, chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta and rhinitis sicca, rhinitis medicamentosa, membranous rhinitis including croupous, fibrinous and pseudomembranous rhinitis, scrofulous rhinitis, seasonal rhinitis including rhinitis nervosa (hay fever) and vasomotor rhinitis. Of particular interest are allergic rhinitis and seasonal rhinitis including rhinitis nervosa (hay fever). The compounds are also indicated for the treatment of nasal polyps and allergic menifestations of the nasopharynx other than those described hereintofore.

The compounds of the invention are also indicated the treatment or prevention of allergic, inflammatory or auto-immune conditions of the eye such as conjunctivitis (allergic, acute, vernal, of hay fever, chronic), inflammation disorders of the eyelids, cornea, uveal tract and retina.

The compounds of the invention are also indicated in the treatment and prevention of allergic, inflammatory and auto-immune conditions of the gastrointestinal tract such as food allergy and food intolerance, ulcerative colitis, Crohn's disease, irritable bowel disease, gastric ulcers, and food related allergic diseases which have symptomatic manifestations remote from the gastrointestinal tract, for example migraine, rhinitis and eczema.

The compounds of the invention are indicated for use in the treatment or prevention of allergic, inflammatory or auto-immune conditions of the skin such as psoriasis, atopical dermatitis, contact dermatitis/dermatitis herpetiformis, erythema nodosum, urticaria, cutaneous eosinophilias, acne, Alopecia areata, eosinophilic fascitis dermatomyositis, photoallergic sensitivity and periodontal disease.

The compounds of the invention are therefore indicated for use in the treatment or prevention of allergic, inflammatory or auto-immune conditions of the joints and

connective tissue, including osteoarthritis, rheumatoid arthritis, systemic lupus erythematosis, vasculitis, Wegener's granulomatosis, polyarthritis nodosa, bursitis, tendonitis, gout, Behcet's syndrome, ankylosing sponditis, Reiter's syndrome and psoriatic arthritis.

The compounds of the invention are indicated in the treatment and prevention of allergic, inflammatory, and auto-immune conditions of the circulatory system including atheroma, reperfusion injury (e.g. on angioplasty), myocardial infarction, thrombosis and vascular and tissue damage caused by ischaemic disease or injury.

The compounds of the invention are indicated in the treatment and prevention of allergic, inflammatory or auto-immune conditions of the CNS including Parkinson's disease, Alzheimers and other dementias, stroke and subarachnoid haemorrhage. The compounds of the invention are indicated in the treatment and prevention of inflammatory conditions of the liver for example hepatitis, cirrhosis and glomerulonephritis.

The compounds of the invention are indicated in the treatment and prevention of allergic, inflammatory or auto-immune conditions of the bladder and uro-genital tract including cystitis.

The compounds of the invention are indicated in the treatment and prevention of tumours and other proliferative diseases.

Of particular interest amongst the above indications is use of the compounds of the invention in a reversible obstructive airways disease, most particularly asthma and especially the treatment and prophylaxis of asthma and rhinitis.

According to a further aspect of the invention there is thus provided the use of a compound of formula I, as hereinbefore defined, or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment of the above diseases, in particular reversible obstructive airways disease, especially the treatment and prophylaxis of asthma and rhinitis.

Administration of the compounds of the invention may be topical (for example by inhalation to the lung). The compounds of the invention may be inhaled as a dry powder which may be pressurised or non-pressurised.

In non-pressurised powder compositions, the active ingredient in finely divided form may be used in admixture with a larger sized pharmaceutically acceptable inert carrier.

The composition may alternatively be pressurised and contain a compressed gas, e.g. nitrogen, or a liquefied gas propellant. In such pressurised compositions, the active ingredient is preferably finely divided. The pressurised composition may also contain a surface active agent. The pressurised compositions may be made by conventional methods. The compounds of the invention may be administered systemically (for example by oral administration to the gastrointestinal tract). The active ingredient may be formulated together with known adjuvants, diluents or carriers using conventional techniques to produce tablets or capsules for oral administration to the gastrointestinal tract.

Examples of suitable adjuvants, diluents or carriers for oral administration in the form of tablets, capsules and dragees include microcrystalline cellulose, calcium phosphate, diatomaceous earth, a sugar such as lactose, dextrose or mannitol, talc, stearic acid, starch, sodium bicarbonate and/or gelatin.

According to a further aspect of the invention there is provided a pharmaceutical composition including a compound of formula I or a salt or solvate thereof as hereinbefore defined in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

Suitable doses for such oral administration are in the range from 0.03 to 30 mg kg^{-1} day^{-1}, for example 3 mg kg^{-1} day^{-1}.

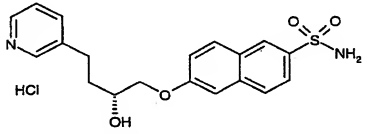
According to a further aspect of the present invention, there is provided a method of treatment or prophylaxis of a reversible obstructive airways disease, in particular asthma, which method comprises administration of a therapeutically effective amount of a compound of formula I as hereinbefore defined, or a pharmaceutically acceptable derivative thereof, to a person suffering from, or susceptible to, the disease.

It will be understood by those skilled in the art that certain functional groups in the compounds of the invention may be protected using appropriate protecting groups as hereinbefore described to form "protected derivatives" of compounds of the invention. All protected derivatives of compounds of formula I are included within the scope of the invention.

The invention is illustrated by the following Examples.

Example 1

(2R)-6-(2-Hydroxy-4-pyridin-3-ylbutoxy)naphthalene-2-sulfonamide, hydrochloride salt



a) 6-Hydroxynaphthalene-2-sulfonic acid *tert*-butyl amide

A solution of 2-naphthol-6-sulfonic acid, sodium salt (10 g) in dry dimethylformamide (100 ml) was cooled to 5°C and thionyl chloride (10 ml) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 30 minutes. *tert*-Butylamine (40 ml) was then added to the reaction dropwise and the mixture stirred under nitrogen for 5hours. The mixture was then poured into 2N hydrochloric acid (500 ml) and extracted into ethyl acetate (3x300 ml). The combined extracts were washed with brine, dried over magnesium sulfate, filtered, and the filtrate concentrated under reduced pressure. The residue was purified by column chromatography over silica, eluting with *iso*hexane/ethyl acetate (2:1) to give the sub-title compound as a solid (1g).

MS (APCI) 278 $(M-H)^+$

^{1}H NMR (DMSO-d6) 10.17(1H, s); 8.28 (1H, s); 7.99-7.96(1H, d); 7.86-7.82(1H, AB); 7.74-7.71(1H, AB); 7.47(1H, s); 7.21-7.17(2H, m); 1.08(9H, s).

b) **(2*R*, 3*E*/*Z*)-4-(3-Pyridyl)-1,2-*O*-*iso*propylidenebut-3-en-1,2-diol**

A solution of *n*-butyllithium (2.5 M in hexanes; 100 ml) was added dropwise to a stirred suspension of 3-pyridylmethyltriphenylphosphonium chloride hydrochloride (53.39 g, *J. Med. Chem.* 1986, 29, 1461) in tetrahydrofuran (50 ml) at -40 °C. The resulting mixture was stirred at room temperature for 30 minutes and was then cooled to -70 °C. A solution of 2,3-*O*-(*S*)-*iso*propylidene-L-glyceraldehyde (15.2 g) (*ex* Oxford Asymmetry; see *Organic Synthesis* (1995) 72, 1) in tetrahydrofuran (10 ml) was added. The resulting mixture was stirred and allowed to reach room temperature over 3 hours. The mixture was

poured into brine (500 ml) and extracted into ethyl acetate. The combined extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography over silica eluting with diethyl ether to give the sub-title compound as an oil (21.2 g).

MS (EI) 205 $(M)^+$

^{1}H NMR ($CDCl_3$) major *Z*-diastereomer 8.53(2H, d); 7.61(1H, dt); 7.29(1H, dd); 6.67(1H, d); 5.85(1H, dd); 4.83(1H, q); 4.16(1H, t); 3.71(1H, t); 1.49(3H, s); 1.39(3H, s).

c) (2R)-4-(3-Pyridyl)-1,2-*O*-*iso*propylidenebutane-1,2-diol

A solution of (2*R*, 3*E*/*Z*)-4-(3-pyridyl)-1,2-*O*-*iso*propylidenebut-3-en-1,2-diol (21.2 g, Example 1b) in ethyl acetate (200 ml) was hydrogenated for 2 hours at 3 atmospheres pressure using palladium on carbon (10%, 0.5 g) as catalyst. The reaction was filtered through celite® and the residue washed with ethyl acetate. The combined filtrate and washings were concentrated under reduced pressure and the residue obtained purified by column chromatography over silica eluting with diethyl ether to give the sub-title compound as an oil (20.5 g).

MS (ESI) 208 $(M + H)^+$

^{1}H NMR ($CDCl_3$) 8.48–8.45(2H, m); 7.52(1H, dt); 7.23(1H, dd); 4.10(1H, quintet); 4.04(1H, t); 3.55(1H, t); 2.84–2.64(2H, m); 1.94–1.80(2H, m); 1.44(3H, s); 1.36(3H, s).

d) (2*R*)-4-(3-Pyridyl)-1,2-butanediol

(2R)-4-(3-Pyridyl)-1,2-*O*-*iso*propylidenebutane-1,2-diol (20.4 g, Example c) was dissolved in hydrochloric acid (2M, 100 ml) and was stirred for 40 minutes. The mixture was neutralised with saturated aqueous sodium hydrogencarbonate solution and was concentrated under reduced pressure. The residue obtained was triturated with ethyl acetate and filtered. The residue was washed with ethyl acetate and the combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue obtained was purified by column chromatography over silica eluting with ethyl acetate : methanol (9:1) to give the sub-title compound as an oil (16.4 g).

MS (APCI) 168 $(M + H)^+$

^{1}H NMR ($CDCl_3$) 8.44–8.40(2H, m); 7.54(1H, d); 7.22(1H, dd); 3.73–3.67(1H, m); 3.65(1H, dd); 3.48(1H, dd); 2.90–2.70(2H, bm); 2.87–2.68(2H, m); 1.84–1.67(2H, m).

e) (2R)-4-[2-(3-Pyridyl)ethyl]-1,3-dioxin-2-one

A solution of (2*R*)-4-(3-pyridyl)-1,2-butanediol (0.42 g, Example d) and 1,1'-carbonyldiimidazole (0.49 g) in chloroform (15 ml) was heated at reflux for 20 minutes. The reaction was cooled and concentrated under reduced pressure. The residue was purified by column chromatography over silica eluting with methanol : dichloromethane (1:19) to give the sub-title compound as an oil (0.35 g).

MS (APCI) 194 $(M + H)^+$

^{1}H NMR ($CDCl_3$) 8.52–8.49(2H, m); 7.53(1H, d); 7.26(1H, dd); 4.73–4.66(1H, m); 4.54 (1H, dd); 4.09 (1H, dd); 2.94-2.88 (1H, m); 2.86-2.72 (1H, m); 2.17-2.09 (1H, m); 2.02-1.97 (1H, m).

f) (2R)-6-(2-Hydroxy-4-pyridin-3-ylbutoxy)naphthalene-2-sulfonic acid *tert*-butyl amide.

A mixture of (2R)-4-[2-(3-pyridyl)ethyl]-1,3-dioxin-2-one (Example 1e, 1.33 g), 6-hydroxynaphthalene-2-sulfonic acid *tert*- butyl amide (Example 1a, 1.6 g), cesium carbonate (2.25 g) and dimethyl formamide (25 ml) were heated together at 100°C, under nitrogen, for 20 hours. The mixture was then cooled, poured into water (200 ml) and extracted into ethyl acetate (3 x 200 ml). The combined extracts were washed with brine, dried over magnesium sulfate, filtered, and the filtrate concentrated under reduced pressure. The residue was purified by column chromatography over silica eluting with ethyl acetate to give the sub-title compound (1.17 g).

MS (APCI) 429 $(M+H)^+$

^{1}H NMR ($CDCl_3$) 8.54-8.53(1H, d); 8.49-8.46(1H, dd); 8.36(1H, s); 7.87-7.80(3H, m); 7.59-7.56(1H, m); 7.27-7.15(3H, m); 4.53(1H, s); 4.13-4.01(3H, m); 2.96-2.75(2H, m); 2.46(1H, s); 1.98-1.93(2H, m); 1.24(9H, s).

g) (2R)-6-(2-Hydroxy-4-pyridin-3-ylbutoxy)naphthalene-2-sulfonic acid amide, hydrochloride salt

(2R)-6-(2-Hydroxy-4-pyridin-3-ylbutoxy)naphthalene-2-sulfonic acid *tert*-butyl amide (Example 1f, 1.17 g), trifluoroacetic acid (12 ml) and dry dichloromethane (12 ml) were stirred together at room temperature, under nitrogen, for 20 hours. The reaction mixture was then concentrated under reduced pressure. To the residue was added methanol (5 ml) and aqueous ammonia solution (5 ml, 10%w/v) and the mixture stirred for 10 minutes. The methanol was removed in vacuo and the resulting aqueous solution was extracted into ethyl acetate (3 x 50 ml), dried over magnesium sulfate, filtered, and the filtrate concentrated under reduced pressure. The residue was purified by column chromatography over silica, eluting with 2% methanol in dichloromethane to give the title compound as its free base.

MS (APCI) 373 $(M+H)^+$

^{1}H NMR (DMSO-d6) 8.48-8.47(1H, d); 8.41-8.38 (1H, dd); 8.33(1H, d); 8.05-8.02(1H, d); 7.98-7.95(1H, d); 7.83-7.82(1H, d); 7.80-7.79(1H, d); 7.69-7.65(1H, m); 7.43-7.42 (1H, d); 7.35-7.28 (4H, m); 5.14-5.12 (1H, d); 4.06-4.04 (2H, d); 3.89-3.84 (1H, m); 2.87-2.64 (2H, m); 1.94-1.71 (2H, m).

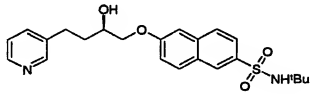
The hydrochloride salt was formed by dissolving the free base in hot methanol (50 ml) and adding 6N ethanolic hydrogen chloride. The resulting white solid was filtered off and dried in vacuo

MS (APCI) 373 $(M+H-HCl)^+$

^{1}H NMR (DMSO-d6) 8.82(1H, s); 8.73-8.72 (1H, d); 8.42-8.39(1H, d); 8.33(1H, s); 8.06-7.80(4H, m); 7.44-7.43(1H, d); 7.36(2H, s); 7.31-7.27(1H, dd); 4.07-4.05(2H, d); 3.92-3.85(1H, m); 3.04-2.84 (2H, m); 2.03-1.77 (2H, m).

Example 2

6-(2-hydroxy-4-pyridin-3-yl-butoxy)-naphthylene-2-sulfonyl *tert*-butylamide (alternative procedure)



4-(2-Pyridin-3-yl-ethyl)-[1,3]dioxolan-2-one oxalate (36.6g, 0.13mol) was dissolved in 290ml NMP. Imidazole (18g, 0.26mol) was added and the line washed with NMP (12ml). The reaction was stirred at rt for 2 hours. The resulting insoluble imidazole oxalate salt was removed by filtration and the cake washed with NMP (3x20ml). The hydroxy-naphthalene (2) (36g, 0.13mol) was added to the filtrate, washed in with NMP (42ml), followed by cesium carbonate (18g, 0.06mol) also washed in with NMP (42ml). The reaction was heated at 100°C for approximately 20 hours, and then cooled to ambient temperature. 2M $HCl_{(aq)}$ (481ml) was added cautiously, producing an exotherm of approximately 15°C and vigorous effervescence. Water (1L) was added and the solution was extracted into ethyl acetate (3x800ml). The aqueous layer was basified using 2M NaOH (842ml) and the product was extracted into ethyl acetate (3x800ml). This solution was concentrated to give a brown oil, which was washed with water (1800ml) and ethyl acetate (200ml) to remove residual NMP, and extracted into ethyl acetate (2x400ml). The ethyl acetate solution was dried and concentrated to yield the desired sulphonamide naphthalene alcohol product (3) (46g, 84%) as a foam.

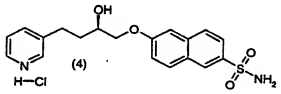
LC/MS : mass 429.1 (M+)

HPLC Purity : 89.6%

^{1}H NMR : δ_H 1.15 (9H, s, NH(CH_3)$_3$), δ_H 1.9 (2H, m, PyCH_2CH_3), δ_H 2.7 (2H, m, PyCH_2CH_2), δ_H 3.9 (1H, m, PyCH_2CH_2CHOH), δ_H 4.06 (2H, d, J5.9, PyCH_2CH_2CH(OH)CH_2), δ_H 5.2 1H, d, J7.4, PyCH_2CH_2CH(O**H**)), δ_H 7.27, (1H, m, Np**H**), δ_H 7.29, (1H, m, Py**H**), δ_H 7.4 (1H, d, J2.2, Np**H**), δ_H 7.5 (1H, S, SO_2N**H**(CH_3)$_3$), δ_H 7.65 (1H, d, J7.8, Py**H**), δ_H 7.8, (1H, dd, J8.8, J1.4, Np**H**), δ_H 7.9 (1H, d, J8.9, Np**H**), δ_H 8.06

(1H, d, J8.8, NpH), δ_H 8.3, (1H, d, J1.2, NpH), δ_H 8.4 (1H, dd, J4.5, J1.3, PyH), δ_H 8.49 (1H, d, J2.5, PyH)

(2R)-6-(2-Hydroxy-4-pyridin-3-ylbutoxy)naphthalene-2-sulfonamide hydrochloride salt



(4)

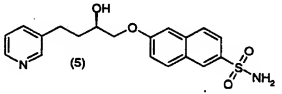
6-(2-hydroxy-4-pyridin-3-yl-butoxy)-naphthylene-2-sulfonyl *tert*-butylamide (46g, 0.11mol) was suspended in MeOH (370ml) and concentrated HCl (185ml) was added. The solution was heated at reflux for 18 hours and then allowed to cool to rt. The solid crystalline product began to precipitate from the reaction mixture at approximately 40°C. Ethyl acetate (400ml) was added and the slurry was allowed to stir for 2 hours to remove any trace of the regioisomer (6). The product was collected by filtration and dried in a vacuum oven to yield the desired AR-C125630AA (4) (29g, 66%).

LC/MS : mass 373.1 (M+)

HPLC Purity : 99.8%

^{1}H NMR : δ_H 1.97 (2H, m, $PyCH_2CH_2$), δ_H 3.9 (2H, m, $PyCH_2$), δ_H 3.9 (1H, m, $PyCH_2CH_2CH(OH)$), δ_H 4.1 (2H, d, J6.7, $CH(OH)CH_2$), δ_H 7.2 (1H, d, J7.4, NpH), δ_H 7.4 (2H, s, SO_2NH_2), δ_H 7.5 (1H, s, NpH) δ_H 7.8 (1H, d, J7.4, PyH) δ_H 8.0 (2H, m, PyH+NpH), δ_H 8.05 (1H, d, J7.8, NpH), δ_H 8.3 (1H, s, NpH), δ_H 8.5 (1H, d, J7.4, NpH), δ_H 8.8 (1H, d, J6.7, PyH), δ_H 8.9 (1H, s, PyH)

6-(2-Hydroxy-4-pyridin-3-ylbutoxy)naphthalene-2-sulfonamide



(5)

(2R)-6-(2-Hydroxy-4-pyridin-3-ylbutoxy)naphthalene-2-sulfonamide hydrochloride salt (158g, 0.39mol) was suspended in methanol (1L). 1M NaOH (406ml, 0.39mol, 1 molar equivalent) was added and the whole stirred at rt for 2 hours. Water (1375ml) was added to the resulting slurry and the mixture stirred for a further hour. The crystalline product was isolated by filtration and the cake washed with 9:1 water:methanol (680ml). The white crystalline product was then dried in a vacuum oven to yield AR-C125630XX (5) (140g, 97%)

LC/MS : 373 mass (M+)

HPLC Purity : 99.8%

^{1}H NMR : δ_H 1.9 (2H, m, PyCH$_2$CH$_2$), δ_H 2.7 (2H, m, PyCH$_2$), δ_H 3.88 (1H, m, CH(OH)H), δ_H 4.06 (2H, d, J7.4, CH(OH)CH$_2$), δ_H 5.1 (1H, d, J6.2, CH(OH)), δ_H 7.3 (1H, dd, J2.8, J6.5, NpH), δ_H 7.3 (1H, d, J2.1, PyH), δ_H 7.35 (2H, s, NH$_2$), δ_H 7.45 (1H, d, J2.5, NpH), δ_H 7.7 (1H, d, J6.1, PyH), δ_H 7.83 (1H, d, J2.2, J8.8, NpH), δ_H 7.95 (1H, d, J8.5, NpH,), δ_H 8.0 (1H, d, J8.4, NpH), δ_H 8.35 (1H, d, J1.1, NpH), δ_H 8.4 (1H, d, J3.1, PyH), δ_H 8.5 (1H, d, J1.0, PyH)

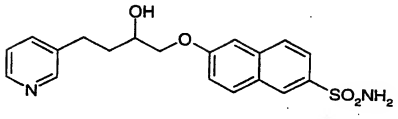
Pharmacological activity

The pharmacological activity of the compounds of the invention may be tested by the method of E. Wells *et al*, 'Characterization of primate bronchoalveolar mast cells: II—inhibition of histamine, LTC_4 and PGD_2 release from primate bronchoalveolar mast cells and a comparison with rat peritoneal mast cells', *J. Immunol.*, vol. 137, 3941, 1986.

The compound exemplified were tested and found to inhibit histamine release at a concentration of less than 10^{-4} M (IC_{50}).

Claims

1. A compound of formula (I) or a salt or solvate thereof:



(I)

2. A compound according to claim 1 which is:
(2R)-6-(2-hydroxy-4-pyridin-3-ylbutoxy)naphthalene-2-sulfonic acid amide,
or a salt or solvate thereof.

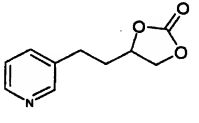
3. A compound according to claim 1 or 2 for use in therapy.

4. Use according to claim 3 wherein the disease is asthma or rhinitis.

5. A pharmaceutical composition comprising a compound of formula (I) or a salt or solvate thereof as defined in claim 1 or 2 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

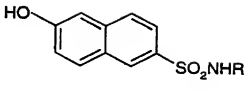
6. A method of treatment or prophylaxis of a reversible obstructive airways disease, in particular asthma, which method comprises administration of a therapeutically effective amount of a compound of formula I as hereinbefore defined, or a pharmaceutically acceptable derivative thereof, to a person suffering from, or susceptible to, the disease.

7. A process for the preparation of compounds of formula (I) which comprises:
(a) reaction of a compound of formula (II):



(II)

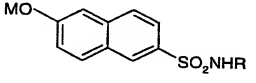
with a compound of formula (III):



(III)

where R is a suitable protecting group, or

(b) reaction of (±)-3-(2-oxiranylethyl)pyridine or α-(chloromethyl)-3-pyridinepropanol either with a compound of formula (IV):



(IV)

where R is as defined above and where M is Li, Na, K or MgHal where Hal is halogen; or with a compound of formula (II) as defined above in the presence of a base, and optionally thereafter (a) or (b):

- removing any protecting groups, and/or
- forming a pharmaceutically acceptable salt.

8. A compound of formula (III) as defined in claim 7.

9. 6-(2-hydroxy-4-pyridin-3-yl-butoxy)-naphthylene-2-sulfonyl *tert*-butylamide:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/01630

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 213/30, A61K 31/44
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9720815 A1 (ASTRA PHARMACEUTICALS LTD. ET AL), 12 June 1997 (12.06.97) -- ---------	1-5,7,9

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention.
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 January 2000	22 -01- 2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson/ELY Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE98/01070

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 6
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.1.

2. ☒ Claims Nos.: 8
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Product claim 8 is indefinite due to the expression "R is a suitable protection group" and has therefore not been searched. According to PCT Article 6, the claims shall be clear and concise.

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/12/99

International application No.
PCT/SE 99/01630

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9720815 A1	12/06/97	AU 1048097 A	27/06/97
		BR 9611555 A	02/03/99
		CN 1208403 A	17/02/99
		CZ 9801724 A	16/12/98
		EP 0865431 A	23/09/98
		GB 9524920 D	00/00/00
		HU 9900143 A	28/05/99
		NO 982566 A	24/07/98
		NZ 323521 A	28/10/99
		SK 73998 A	11/02/99
		US 5977105 A	02/11/99
		GB 9609403 D	00/00/00
		GB 9622412 D	00/00/00
		PL 327054 A	23/11/98